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TOWNSEND and TOWNSEND and CREW LLP

By: Rosmarie L. Celli

PATENT
Attorney Docket No.: 15270J-004740US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Schenk, Dale B.

Application No.: 09/322,289

Filed: May 28, 1999

For: PREVENTION AND TREATMENT OF AMYLOIDOGENIC DISEASE

Customer No.: 20350

Confirmation No. 7773

Examiner: Kolker, Daniel E.

Technology Center/Art Unit: 1649

DECLARATION OF SHYRA J. GARDAI UNDER 37 C.F.R. § 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Shyra J. Gardai state, as follows:

1. My current position is a scientist at Elan Pharmaceuticals, Inc (Elan). I understand the above application is assigned to Elan or one of its affiliated companies.

2. I have a B.S. in biochemistry/microbiology from the University of Idaho (1997), and a Ph.D. in Innate Immunology from the University of Colorado Health Sciences Center (2002). A list of my publications is attached. One of my responsibilities at Elan has been to perform experiments comparing antibodies having different isotypes. In the course of my studies and subsequently as a scientist, I have read many texts of immunology, read the scientific literature, particularly that relating to my own work, and have attended and presented at conferences relating to my work.

3. I understand that the Examiner of the above application is taking the view that there is a general rule well known to those in the field that an antibody having a human IgG1 isotype binds more strongly to an antigen than an otherwise identical antibody having another human IgG isotype. However, I have no recollection of having heard of such a general proposition before. Based on my experience and knowledge of the scientific literature, there are some instances where one human IgG isotype may bind more strongly than other isotypes, but these are dependent on a particular antibody or antigen. I have reviewed WO 91/16928, which I understand the Examiner is citing as a basis for his position. I read this reference as reporting an example in which a particular antibody has higher avidity in the human IgG1 isoform but not as establishing a general rule. I am aware of another reference McClosekey et al., Immunology 88, 169-173 (1996) reporting the order of dissociation rate constants for human isotypes as being IgG4 less than IgG3 less than IgG2 less than IgG1. Because the on-rate constants for the different isotypes were similar (see Table 1), a lower dissociation rate constant translates into a higher binding strength (i.e., human IgG4 has the highest binding strength and human IgG1 the weakest binding strength). To reiterate, however, both McClosekey and WO 91/16927 are just examples, and I have not heard of a general rule that antibodies with human IgG1 isotype (or human IgG4) bind more strongly than other human IgG isotypes irrespective of a particular antibody or antigen. I believe based on my knowledge and experience, such a rule would not be accurate.

4. In selecting a human isotype for a humanized antibody, I would be most interested in the functional properties of the different isotypes and their relevance to the proposed mechanism of the antibody. I would not assume a priori there was any meaningful difference in affinity between different human IgG isotypes, and unless a substantial difference in binding strength was demonstrated experimentally for a particular antibody, possible variations in binding

strength would not be a significant factor in selecting a human IgG isotype. If a significant difference in binding strength between isotypes was demonstrated for a particular antibody, it would still not be determinative for isotype selection, but I would take affinity into account together with other functional properties in selecting an isotype.

5. Different nomenclature is used for human and mouse IgG isotypes. The human isotypes are referred to as IgG1, IgG2, IgG3 and IgG4. The mouse isotypes are referred to as IgG1, IgG2a, IgG2b and IgG3. The different isotypes differ in a number of functional properties including complement activation, Fc gamma receptor binding, and mast cell binding. Although there is no single human isotype having identical functional properties to a mouse isotype, there is a similarity between particular human isotypes and corresponding mouse isotypes. The isotype correspondence between human and mouse isotypes does not follow simply from their respective names. For example, human IgG1 is not the closest human equivalent of mouse IgG1. The human IgG1 isotype has the properties of strongly interacting with complement and Fc gamma receptors. The most similar mouse isotype is mouse Ig2A. Mouse IgG1 interacts substantially less well with complement and Fcgamma receptors. The most similar human isotypes are IgG2 and IgG4. Mouse IgG1 also shares the property of human IgG4 of binding to mast cells. If I were selecting an isotype for a humanized version of a mouse IgG1 antibody and wanted the human isotype to perform most similarly to the mouse antibody, I would therefore select a human IgG2 or IgG4 isotype.

6. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States

Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

Shyra J. Gardai

Date: 3/2/09

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Publication list

1: Surfactant proteins A and D suppress alveolar macrophage phagocytosis via interaction with SIRP alpha. Janssen WJ, McPhillips KA, Dickinson MG, Linderman DJ, Morimoto K, Xiao YQ, Oldham KM, Vandivier RW, Henson PM, Gardai SJ. Am J Respir Crit Care Med. 2008 Jul 15;178(2):158-67. Epub 2008 Apr 17.

2: Apoptotic cells, through transforming growth factor-beta, coordinately induce anti-inflammatory and suppress pro-inflammatory eicosanoid and NO synthesis in murine macrophages. Freire-de-Lima CG, Xiao YQ, Gardai SJ, Bratton DL, Schiemann WP, Henson PM. J Biol Chem. 2006 Dec 15;281(50):38376-84. Epub 2006 Oct 20.

3: ATP-binding cassette transporter A7 enhances phagocytosis of apoptotic cells and associated ERK signaling in macrophages. Jehle AW, Gardai SJ, Li S, Linsel-Nitschke P, Morimoto K, Janssen WJ, Vandivier RW, Wang N, Greenberg S, Dale BM, Qin C, Henson PM, Tall AR. J Cell Biol. 2006 Aug 14;174(4):547-56.

4: Recognition ligands on apoptotic cells: a perspective. Gardai SJ, Bratton DL, Ogden CA, Henson PM. J Leukoc Biol. 2006 May;79(5):896-903. Review.

5: Cell-surface calreticulin initiates clearance of viable or apoptotic cells through trans-activation of LRP on the phagocyte. Gardai SJ, McPhillips KA, Frasch SC, Janssen WJ, Starefeldt A, Murphy-Ullrich JE, Bratton DL, Oldenborg PA, Michalak M, Henson PM.
Cell. 2005 Oct 21;123(2):321-34.

6: Oxidants inhibit ERK/MAPK and prevent its ability to delay neutrophil apoptosis downstream of mitochondrial changes and at the level of XIAP. Gardai SJ, Whitlock BB, Xiao YQ, Bratton DB, Henson PM. J Biol Chem. 2004 Oct 22;279(43):44695-703. Epub 2004 Jul 30.

7: Phosphorylation of Bax Ser184 by Akt regulates its activity and apoptosis in neutrophils. Gardai SJ, Hildeman DA, Frankel SK, Whitlock BB, Frasch SC, Borregaard N, Marrack P, Bratton DL, Henson PM. J Biol Chem. 2004 May 14;279(20):21085-95. Epub 2004 Feb 6.

8: By binding SIRPalpha or calreticulin/CD91, lung collectins act as dual function surveillance molecules to suppress or enhance inflammation. Gardai SJ, Xiao YQ, Dickinson M, Nick JA, Voelker DR, Greene KE, Henson PM. Cell. 2003 Oct 3;115(1):13-23.

9: Peroxisome proliferator-activated receptor gamma (PPARgamma) expression is decreased in pulmonary hypertension and affects endothelial cell growth. Ameshima S, Golpon H, Cool CD, Chan D, Vandivier RW, Gardai SJ, Wick M, Nemenoff RA, Geraci MW, Voelkel NF. Circ Res. 2003 May 30;92(10):1162-9. Epub 2003 Apr 24.

10: Oxidant-mediated mitochondrial injury in eosinophil apoptosis: enhancement by glucocorticoids and inhibition by granulocyte-macrophage colony-stimulating factor. Gardai SJ, Hoontrakoon R, Goddard CD, Day BJ, Chang LY, Henson PM, Bratton DL. J Immunol. 2003 Jan 1;170(1):556-66.

11: Interleukin-15 inhibits spontaneous apoptosis in human eosinophils via autocrine production of granulocyte macrophage-colony stimulating factor and nuclear factor-kappaB activation. Hoontrakoon R, Chu HW, Gardai SJ, Wenzel SE, McDonald P, Fadok VA, Henson PM, Bratton DL. Am J Respir Cell Mol Biol. 2002 Apr;26(4):404-12.